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COMMENTARY

Herpesviral interplay with peroxisome: An underexplored viral niche

Omkar Indari [a], Süleyman Ergün [b], Srikanth Karnati [b,**], Hem Chandra Jha [a,*]

[a] Department of Biosciences and Biomedical Engineering, Indian Institute of Technology Indore, Simrol, Indore 453552, India
[b] Institute of Anatomy and Cell Biology, Julius-Maximilians-University Würzburg, Würzburg 97070, Germany

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Herpesviruses are smart pathogens that can infect and have lifelong persistence inside the host. Many human herpesviruses have been shown to affect human health in immunologically challenged conditions. Mostly the herpesviruses involved in such cases and widely researched are herpes simplex virus (HSV), human cytomegalovirus (HCMV), Kaposi sarcoma herpesvirus (KSHV), and Epstein-Barr virus (EBV). All these herpesviruses share similar virion structures and life cycles.[1] They possess dynamic mechanisms to manipulate host cell components for entry, immune evasion, replication, gene expression, maintenance of latency, or production of virions by the lytic cycle. Jean Beltran and colleagues reported that herpesviruses are unable to infect cells lacking peroxisomes.[2] The peroxisome is a single membrane-bound organelle that is present in all eukaryotic cells. Their abundance, size, protein composition, and activity can vary according to cell type and stage. Organelle dysfunction related to biogenesis or organelle-driven cellular processes has been linked to developmental disorders, aging, neurological effects, and cancers.[3]

Considering the challenge of maintaining latency or replication to produce virions, herpesviruses could modulate peroxisomes to fulfill the virus's need for lipids for virion assembly and fooling intracellular molecular armors. In this commentary, we provide comprehensive information on herpesvirus-mediated peroxisomal modulation.

Targeting intracellular antiviral response: manipulating host armor for shelter

The role of peroxisomes in antiviral response is linked to mitochondrial antiviral signaling protein (MAVS) (also known as IPS-1, Cardif, and VISA), which has recently been discovered to be present in peroxisomes as well. The HCMV has been shown to target the mitochondrial as well as peroxisomal MAVS using a viral mitochondrial inhibitor of apoptosis (vMIA) which is also identified as pUL37. This interaction hinders the downstream MAVS cascade. Another herpesvirus, HSV-1, has also been shown to disrupt peroxisomal antiviral immunity. HSV-1 structural protein VP16 alters immediate early IFN-stimulated gene expression, possibly targeting the IRF machinery, which is downstream of the MAVS cascade. Interestingly, KSHV has been shown to utilize MAVS for the novel purpose of its latency maintenance. The viral FLICE-inhibitory protein (vFLIP) has been shown to interact with PEX19 as well as MAVS. *PEX19* expression was found to be upregulated in KSHV-infected cells, suggesting that it could help in viral protein interaction with MAVS. Our recent study,

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* Corresponding author.
** Corresponding author.
E-mail addresses: srikanth.karnati@uni-wuerzburg.de (S. Karnati), hemcjha@iiti.ac.in (H. Chandra Jha).

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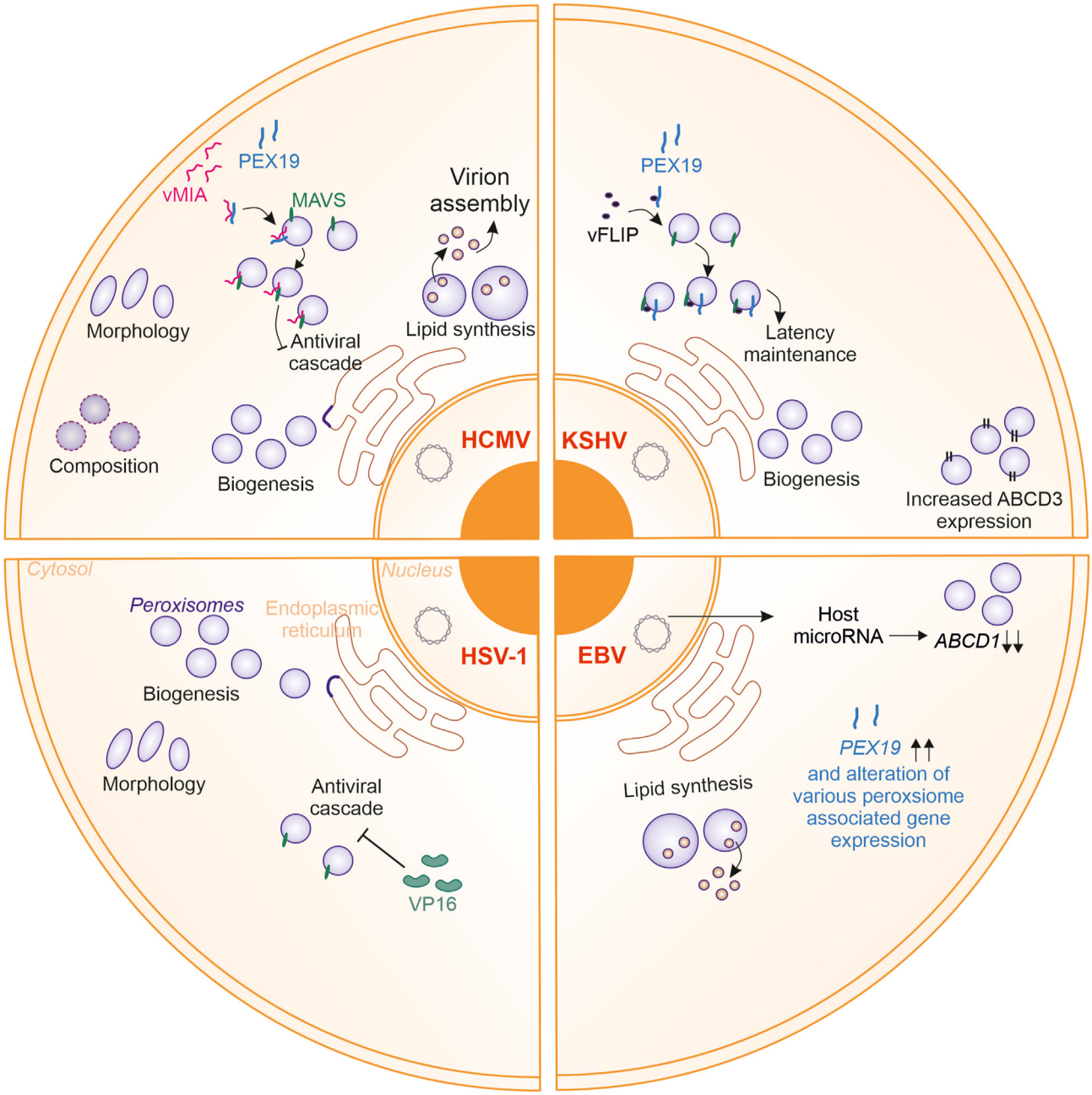

Figure 1 Herpesvirus-mediated peroxisome modulations. The illustration provides an overview of observed prominent alterations of the peroxisomal compartment by respective herpesviruses. HCMV tends to increase peroxisome biogenesis and alter its morphology and protein composition. The HCMV protein viral mitochondrial inhibitor of apoptosis interacts with PEX19 and gets localized at peroxisome where it interacts with MAVS and inhibits antiviral signaling. Similarly, KSHV protein vFLIP is also found to interact with PEX19 and gets localized at peroxisome to interact with MAVS. This interaction was found to be crucial for KSHV latency. HSV-1 has also been shown to increase peroxisome abundance and alter organelle morphology. EBV has been shown to alter various peroxisome-associated genes including PEX19. The EBV was further found to down-regulated ABCD1 expression through host microRNA manipulation.

exploring the impact of acute EBV infection on PBMC, also showed that EBV can induce *PEX19* expression at early time points.[4] Additionally, in agreement with our study, induced *PEX19* expression was observed in a recent report investigating acute EBV infection in B cells.[5] Although its further impacts are yet to be explored, the possibility of the utilization of PEX19 by EBV to initiate interaction with MAVS cannot be neglected.

Viral interference with peroxisomal proteins and lipid metabolism: to eat and grow, or to greet and slow?

The viruses may feed on lipids for utilization in envelope formation and virion production (to eat and grow). Otherwise, the virus may interfere with the proteins or divert

organelle metabolism for the benefit of its stability and maintenance inside the cell (to greet and slow).

HCMV has been shown to increase very long chain fatty acid (VLCFA) synthesis required to produce viral progenies. The virus has also been found to up-regulate PEX protein expression. The up-regulation of these proteins was associated with an increase in peroxisome biogenesis, abundance, as well as lipid, particularly plasmalogen synthesis which is utilized by HCMV for virion assembly.[2] Another report also supported the mechanism of HCMV-mediated PEX3 induction and notified that the viral growth was halted when this induction interfered.[2] Apart from the interplay between HCMV vMIA and PEX19, a recent report also notified continuous vMIA and peroxisome interactions throughout infection. Another herpesvirus HSV-1 also found to elevate peroxisome abundance and modulate morphology and enhance plasmalogen synthesis during the later stages of infection.[2] The KSHV latency-associated region (KLAR) was found to be sufficient to induce ATP-binding cassette subfamily D member (ABCD) 3 expression which further can drive changes in associated lipid metabolism.[2] KSHV has also been reported to elevate peroxisome number and metabolism during latent stages. Interestingly, the proteins ACOX1 and ABCD3, involved in VLCFAs metabolism, were found to be crucial for latent KSHV-infected cell survival. In our recent study, we found that lipid metabolism is distinctly regulated in EBV-transformed Burkitt lymphoma (BL) cells ad during acute EBV infection in peripheral blood mononuclear cells (PBMCs) along with the expression of various peroxisome-associated genes. Specifically, EBV-infected transformed BL cells showed lower lipid abundance, in contrast to the increased lipid abundance observed during the early stages of EBV infection.[4] The study further clarified that EBV-induced host miRNAs lead to *ABCD1* and *ABCD2* down-regulation, leading to the accumulation of VLCFAs. Furthermore, hindering this setup led to reduced viral production, highlighting the importance of this manipulation for this herpesvirus.

Conclusion

Considering the inability of herpesviruses to infect cells lacking peroxisomes, the reliance of these viruses on this cellular organelle is crucial. The peroxisome manipulation by HCMV has been demonstrated frequently with some reports on HSV-1 and KSHV but in slightly different directions. The interplay of EBV with peroxisome is yet unexplored in detail and required thorough investigation considering the association of EBV in multiple pathologies and studies of EBV influence on intracellular lipid levels.[4] The various mechanisms elucidated till now are summarized in Figure 1. Several other bacteria and viruses have also been shown to alter peroxisomal function. Some herpesviruses have been shown to trigger disease severity in cases of co-infections with other pathogens, or other pathogens may induce herpesvirus reactivation. It would be interesting to check how the peroxisomes are exploited during the coinfection of herpesviruses with other herpesviruses or pathogens. More research on herpesvirus-peroxisome interplay could decipher yet unavailable therapeutic targets to inhibit herpesviral growth inside cells.

Conflict of interests

The authors have no conflict of interests.

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